#18
AP/1623

Docket No. 270/030 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Douglas T. Ross et al.

Serial No.: 09/134,419

Filed: August 14, 1998

For: HETEROCYCLIC ESTERS OR AMIDES FOR VISION AND MEMORY DISORDERS

Group Art Unit: 1623

Examiner: H. Owens, Jr.

Office Action mailed:

March 13, 2001

TRANSMITTAL OF APPEAL BRIEF

Hon. Commissioner for Patents
Washington, D.C. 20231

Sir:

Enclosed herewith is an Appellant's Brief (in triplicate) with attached Appendix & Addendum A for the above-identified application.

__X__ The Commissioner is hereby authorized to charge payment of the Appeal Brief fee of $160.00 at the small entity rate, to Deposit Account 12-2475.

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LYON & LYON LLP

April 2, 2002

By _____
James T. Carmichael
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1623

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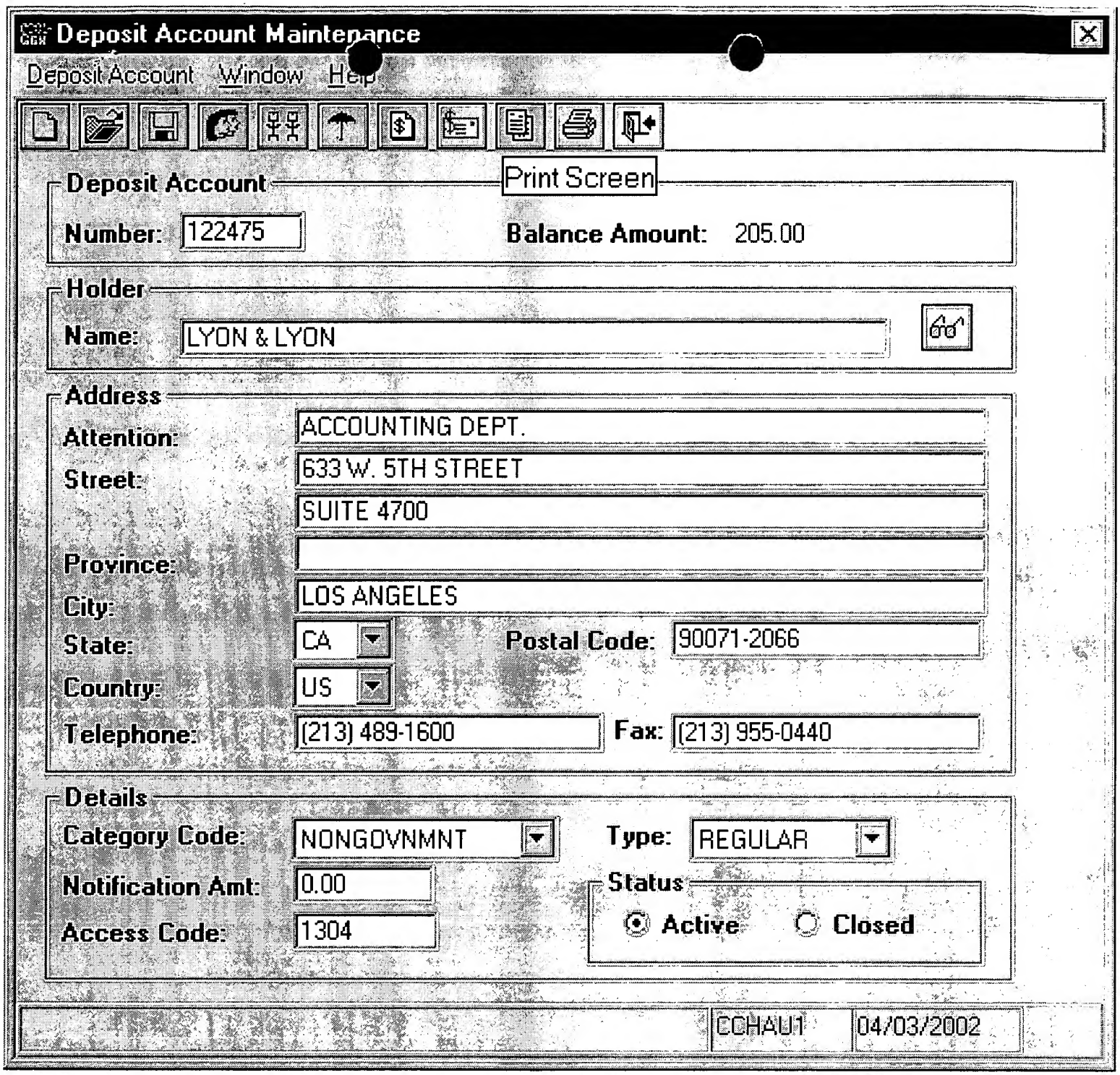
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BRIEF OF APPELLANT

I. Real Party in Interest

The present application is assigned to Guilford Pharmaceuticals Inc.

II. Related Appeals and Interferences

Other pending applications, that are currently on appeal to the Board of Patent Appeals and Interferences and may be considered to be related, include S.N. 09/134,472; S.N. 09/134,421; and S.N. 09/134,422.

III. Status of Claims

Claims 1-4, 6, 8-11, and 21-37 are the only claims pending in the application.[1] All stand finally rejected.

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[1] The cover pages of the Office actions dated October 19, 2001, and March 13, 2001, incorrectly list the pending claims as 1-4, 6, 8, 11, and 21-37. However, the text imposing the final rejection in the March 13, 2001, Office action addresses all of the pending claims, i.e., 1-4, 6, 8-11, and 21-37.

IV. Status of Amendments

An amendment after final rejection was submitted on September 13, 2001, and was refused entry in the Office action dated October 19, 2001. The appended claims reflect entered amendments only.

V. Summary of Invention

The invention is a method for treating a nerve-related vision disorder or treating memory impairment. The method includes administering an effective amount of a nitrogen-containing heterocyclic compound having two or more heteroatoms.

VI. Issues

A. Whether Claims 1-4[2] and 6 were improperly rejected under 35 U.S.C. § 112, second paragraph[3] as failing to particularly point out and distinctly claim the subject matter regarded as the invention?

B. Whether Claims 1-4, 6, 8-11, and 21-37 were improperly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-10, 18-21, and 28-31 of U.S. Patent No. 5,786,378?

C. Whether Claims 1-4, 6, 8-11, and 21-37 were improperly rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,786,378?

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[2] The Office action states that Claims 1-6 were rejected. However, Claim 5 was cancelled.

[3] The Office action states that "Claims 1-6 rejected under 35 U.S.S. [sic] 112(1) has been overcome through applicant's amendment." Final rejection dated March 13, 2001, page 3. Thus, it appears that the reference in the next sentence to 112(1) was unintentional: "Applicant's arguments have been considered, however, the rejection of claims 1-6 under 35 U.S.C. 112(1) and 112(2) is maintained for the reasons of record." Applicants rely on the examiner's indication that the previous rejection under 112(1) was overcome and assume there is no longer any rejection under 35 U.S.C. § 112, first paragraph.

VII. Grouping of Claims

The claims are argued in two groups. The first group consists of Claims 1-4, 8-11, and 21-37. The second group consists of claim 6.

Claim 6 is separately patentable because, as discussed below, it recites that the method is "for improving naturally-occurring vision in an animal, in the absence of any opthalmologic disorder, disease, or injury."

VIII. Argument

A. Claims 1-4 and 6 were improperly rejected under 35 U.S.C. § 112, second paragraph as failing to particularly point out and distinctly claim the subject matter regarded as the invention.

Claims 1-4 and 6 stand rejected as allegedly indefinite for being too broad:

> Given the broad number of compounds which are encompassed by heterocyclic esters applicant should particularly point out and distinctly claim what structure or compound is intended.

Final rejection dated March 13, 2001, page 3. This is not a proper basis for rejection.

The legal standard for definiteness under 35 U.S.C. § 112, second paragraph, is whether a claim reasonably apprises those of skill in the art of its scope. In re Warmerdam, 33 F.3d 1354, 1361, 31 USPQ2d 1754, 1759 (Fed. Cir. 1994). Overbreadth of a claim is not a proper basis for an indefiniteness rejection. In re Hyatt, 708 F.2d 712, 714, 218 USPQ 195, 197 (Fed. Cir. 1983).

In the present case, the examiner has not even asserted that the claims fail to reasonably apprise those of skill in the art of their scope. Those of skill in the art clearly understood what was meant by the claim terms related to esters and heterocyclic compounds. Moreover, the term "heterocyclic esters" mentioned in the rejection no longer appears in the claims, following the entry of the amendment dated November 16, 2000. Because Claims 1-4 and 6 particularly point out and distinctly claim the subject matter regarded as the invention, the rejection under 35 U.S.C. § 112, second paragraph, should be reversed.

B. Claims 1-4, 6, 8-11, and 21-37 were improperly rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-10, 18-21, and 28-31 of U.S. Patent No. 5,786,378.

An obviousness-type double patenting rejection must establish that the present invention was merely an obvious variation of the subject matter defined by a claim in an issued patent. In re Braat, 937 F.2d 589, 592, 19 USPQ2d 1289, 1292 (Fed. Cir. 1991).

In the present case, the '378 patent claims use of a compound to treat certain groups of disorders, and the appealed claims recite instead the treatment of vision disorders or memory impairment. According to the examiner, the motivation or suggestion to make the required changes and arrive at the invention of the appealed claims was that the '378 patent claims use of the compound to treat or effect neuronal activity, and therefore it would have been *per se* obvious to use the compound to treat any condition having a neurological basis:

> Given that the claims of '378 are drawn to treating or effecting neuronal activity via stimulation of damaged neurons, promotion of neuronal regulation and treatment of a neurological disorder using the same compounds set forth in the instant application, one of skill in the art would certainly have a reasonable expectation of success in the use of these compounds to treat conditions which have a neurological basis as well as be provided with the motivation to use these compounds for disorders which have a neurological etiology.

Final rejection dated March 13, 2001, page 3. Such a *per se* rejection fails to establish the required motivation or suggestion in the prior art. There is no evidence of record that one of ordinary skill in the art expected a compound effective for certain groups of neurological disorders to be effective for every other neurological disorder, or for vision disorders or memory impairment. The examiner's *per se* rejection should be reversed for failing to state a *prima facie* case of obviousness.

Moreover, the examiner incorrectly looked to the patent claims for what they disclose, rather than for what they claim. In the context of an obviousness-type double patenting analysis, the patented claim must be considered as a whole for what it claims, not for what it discloses. General Foods Corp. v. Studeingesellschaft Kohle mbH, 972 F.2d 1272, 1274, 23 USPQ2d 1839, 1840 (Fed. Cir. 1992). In that case, the patented claim was for a process having nine steps, one of the steps being "the essence of the very same process" in the challenged claim. The court held that it was error to view the one

step as a prior art reference, finding that the subject matter of the challenged claim was not suggested by the nine-step process:

> Our precedent makes clear that the *disclosure* of a patent cited in support of a double patenting rejection cannot be used as though it were prior art, *even where the disclosure is found in the claims.*

Id. at 1281, 23 USPQ2d at 1846.

In the present case, the '378 patent claims as whole define a method of effecting a neuronal activity which may be any one of stimulating damaged neurons, promoting neuronal regeneration, or treating a neurological disorder. Thus, in the claimed method, the recited compound may or may not treat a neurological disorder. Neurological disorders that may be treated include peripheral neuropathy caused by physical injury or disease state, physical damage to the brain, physical damage to the spinal cord, stroke associated with brain damage, and neurological disorders related to neurodegeneration. Thus, in the claimed method, if the recited compound is used to treat a neurological disorder, it may treat any one of those five disorders. If, from among those five disorders, the claimed method treats a neurological disorder relating to neurodegeneration, it may treat any one of Alzheimer's Disease, Parkinson's Disease, and amyotrophic lateral sclerosis. The patented claims do not further specify any particular disease.

Had the examiner considered the patent claims as a whole as required by General Foods, he would have realized that they cover using a compound to treat one of a large number of disorders, many of which have nothing to do with vision or memory. There is

no prior art evidence that such a compound would be useful for treating memory disorders or vision impairments.

Because the rejection does not set forth a *prima facie* case of obviousness, the Board need not consider the rebuttal evidence submitted by Appellants. However, if the examiner were to provide *prima facie* evidence that a compound useful in treating certain neurological disorders was expected successfully to treat every other neurological disorder, it would be rebutted by the evidence that is of record.

The record reflects that compounds such as Imipramine used for treating symptoms associated with Alzheimer's Disease are not effective for treating memory impairment, and there is also no expectation that such compounds would be effective in treating vision disorders. Teri et al., J. Gerontology, 46 (1991) 372-377 (copy attached as Addendum A). In fact, the researchers postulate that higher dosages of Imipramine effective for treating depression associated with Alzheimer's Disease may actually affect cognition adversely. Id. at 376. However, since the examiner has not even attempted to relate the '378 patent claims to the specific disorders recited in the appealed claims, the rejection may be reversed on that basis alone.

Regardless, claim 6 of the present application is separately patentable because it recites that the method is "for improving naturally-occurring vision in an animal, in the absence of any opthalmologic disorder, disease, or injury." The examiner has not even attempted to address these limitations, and the rejection must be reversed as failing to establish a *prima facie* case of obviousness. No patented claim is cited that deals with or suggests improving naturally-occurring vision in the absence of any opthalmologic disorder, disease, or injury.

C. Claims 1-4, 6, 8-11, and 21-37 were improperly rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 5,786,378.

The § 103 rejection over the teachings of the '378 patent should be reversed for the same reasons stated above with respect to the obviousness-type double patenting rejection and the following additional reasons. The only motivation or suggestion identified by the examiner is that the references teach treatment of neurological disorders:

> A person of ordinary skill in the art would have been motivated to use the analogous compounds for the treatment of nerve related vision disorders or memory impairments given the general use of these compounds in the prior art for stimulation of damaged neurons, promotion of neuronal regulation and treatment of neurological disorders; as well as the non-immunosuppressive activity displayed by these compounds.

Final rejection dated March 13, 2001, page 5. The prior art's treatment of some neurological disorders does not suggest that the recited compound would work for any and every other neurological disorder.

Moreover, nothing in the cited art mentions the specific conditions recited in the present claims, let alone suggests treating them with the recited compound. The examiner asserts that the '378 patent teaches "treatment of memory impairment such as Alzheimer's disease." That assertion is factually incorrect. Alzheimer's Disease is not a

memory impairment, and nothing in the cited reference suggests that it is. In fact, nothing in the cited reference even mentions memory.

There is no evidence of record that a compound useful for Alzheimer's Disease, Parkinson's Disease, and the other conditions mentioned in the cited references was expected to work for vision disorders or memory impairment. Without such evidence, the rejection must fail:

> With respect to core factual findings in a determination of patentability, however, the Board cannot simply reach conclusions based on its own understanding or experience—or on its assessment of what would be basic knowledge or common sense.

In re Zurko, 238 F. 3d 1379, 1385-86, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001); In re Lee, Appeal No. 00-1158, 61 USPQ2d 1430, 1435 (Fed. Cir. Jan. 18, 2002).

The examiner may have some personal unstated understanding regarding a relationship between Alzheimer's Disease and memory impairment. However, the examiner provides no evidence regarding such relationship. No cited reference mentions memory impairment. No cited reference mentions vision disorders. Lacking evidence, the rejection is improper under Zurko and Lee.

Because the rejection does not establish a *prima facie* case of obviousness, the Board need not consider the rebuttal evidence submitted by Appellants. However, if the examiner were to provide *prima facie* evidence that a compound useful in treating certain neurological disorders was expected successfully to treat vision disorders or memory impairments, it would be rebutted by the evidence that is of record.

The record reflects that compounds such as Imipramine used for treating symptoms associated with Alzheimer's Disease are not effective for treating memory impairment, and there is also no expectation that such compounds would be effective in treating vision disorders. Teri et al., J. Gerontology, 46 (1991) 372-377 (copy attached as Addendum A). In fact, the researchers postulate that higher dosages of Imipramine effective for treating depression associated with Alzheimer's Disease may actually affect cognition adversely. Id. at 376. Clearly, a compound was not expected to work on vision disorders or memory impairment merely because it was thought to work on a group of diseases that encompassed Alzheimer's Disease.

In any event, Claim 6 is separately patentable because it recites that the method is "for improving naturally-occurring vision in an animal, in the absence of any opthalmologic disorder, disease, or injury." The examiner has not even attempted to address these limitations, and the rejection must be reversed as failing to establish a *prima facie* case of obviousness. No reference is cited that deals with or suggests improving naturally-occurring vision in the absence of any opthalmologic disorder, disease, or injury.

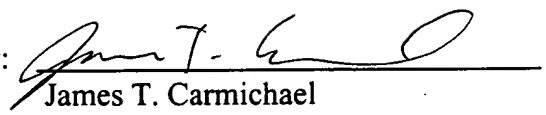
IX. Conclusion

The rejections of Claims 1-4, 6, 8-11, and 21-37 should be reversed for the reasons stated.

For the Appellant:

LYON & LYON LLP

Dated: April 2, 2002

By: 
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CLAIMS

1. A method for treating a nerve-related vision disorder or treating memory impairment in a mammal in need thereof, which comprises administering to said mammal an effective amount of a nitrogen-containing heterocyclic compound having two or more heteroatoms,

wherein said compound has an N-linked substituent selected from the group consisting of -C(W)-C(Y)-

wherein W and Y are independently selected from the group consisting of O, S, CH_2, and H_2,

wherein said compound is additionally substituted with a ester or amide substituent attached to the heterocyclic ring, and

wherein the nerve-related vision disorder is selected from the group consisting of the following:

visual impairments;

orbital disorders;

disorders of the lacrimal apparatus;

disorders of the eyelids;

disorders of the conjunctiva;

disorders of the cornea;

cataract;

disorders of the uveal tract;

disorders of the retina;

disorders of the optic nerve or visual pathways;

free radical induced eye disorders and diseases;

immunologically-mediated eye disorders and diseases;

nerve-related physical injury affecting vision;

nerve related symptoms and complications of eye disease, nerve-related symptoms and complications of eye disorders, and nerve-related symptoms and complications of physical injury affecting vision.

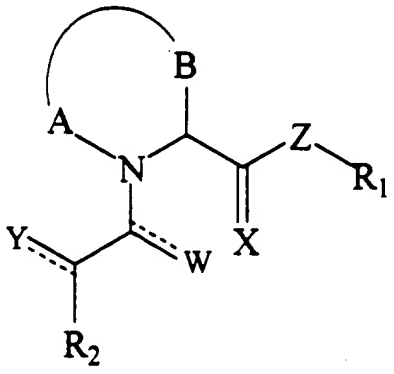
2. The method of claim 1, wherein the compound is immunosuppressive.

3. The method of claim 1, wherein the compound has an affinity for an FKBP-type immunophilin.

4. The method of claim 3, wherein the FKBP-type immunophilin is FKBP-12.

6. The method of claim 1, which is for improving naturally-occurring vision in an animal, in the absence of any opthalmologic disorder, disease, or injury.

7. *(Cancelled)* The method of claim 1, wherein the compound is of Formula I



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or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring

containing, in addition to the nitrogen atom, one or more additional O, S, SO, SO_2, N, NH, or NR_1 heteroatom;

X is O or S;

Z is O, NH, NR_1, or a bond

W and Y are independently O, S, CH_2, or H_2;

R_1 is C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl, which is substituted with one or more substituent(s) independently selected in one or more position(s) with $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

R_2 is either C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl or Ar_1, wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy; and

Ar_1 and Ar_2 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring, wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino; wherein the individual ring size is 5-6 members; and wherein the heterocyclic

ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

8. The method of claim 7, wherein the mono- or bicyclic, carbo- or heterocyclic ring is selected from the group consisting of naphthyl, indolyl, furyl, thiazolyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, fluorenyl, and phenyl.

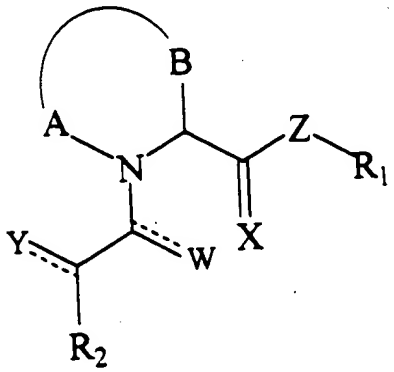
9. The method of claim 7, wherein the one or more additional heteroatom(s) in the 5-7 membered saturated or unsaturated heterocyclic ring is NH or NR_1.

10. The method of claim 1, wherein the vision disorder is selected from the group consisting of: visual impairments; orbital disorders; disorders of the larcimal apparatus; disorders of the eyelids; disorders of the conjunctiva; disorders of the cornea; cataract; disorders of the uveal tract; disorders of the retina; disorders of the optic nerve or visual pathways; free radical induced eye disorders and diseases; immunologically-mediated eye disorders and diseases; eye injuries; and symptoms and complications of eye disease, eye disorder, or eye injury.

11. The method of claim 10, wherein vision regeneration is undertaken to improve naturally-occurring vision in an animal, in the absence of any opthalmologic disorder, disease, or injury.

21. The method of claim 1, wherein the compound is non-immunosuppressive.

22. The method of claim 1, wherein the compound is of formula I



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or a pharmaceutically acceptable salt, ester, or solvate thereof, wherein:

A and B, together with the nitrogen and carbon atoms to which they are respectively attached, form a 5-7 membered saturated or unsaturated heterocyclic ring containing, in addition to the nitrogen atom, one or more additional O, S, SO, SO_2, N, NH, or NR_1 heteroatom(s);

X is O or S;

Z is O, NH, NR_1, or a bond;

W and Y are independently O, S, CH_2, or H_2;

R_1 is C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl, which is substituted in one or more position(s) with one or more substituent(s) independently selected from the group consisting of $(Ar_1)_n$, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with $(Ar_1)_n$, C_3-C_8 cycloalkyl, C_1-C_6 straight or branched chain alkyl or C_2-C_6 straight or branched chain alkenyl substituted with C_3-C_8 cycloalkyl, and Ar_2;

n is 1 or 2;

R_2 is C_1-C_9 straight or branched chain alkyl, C_2-C_9 straight or branched chain alkenyl, C_3-C_8 cycloalkyl, C_5-C_7 cycloalkenyl or Ar_1,

wherein said alkyl, alkenyl, cycloalkyl or cycloalkenyl is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of C_1-C_4 straight or branched chain alkyl, C_2-C_4 straight or branched chain alkenyl, and hydroxy; and Ar_1 and Ar_2 are independently an alicyclic or aromatic, mono-, bi- or tricyclic, carbo- or heterocyclic ring,

wherein the ring is either unsubstituted or substituted with one or more substituent(s) independently selected from the group consisting of halo, hydroxy, nitro, trifluoromethyl, C_1-C_6 straight or branched chain alkyl, C_2-C_6 straight or branched chain alkenyl, C_1-C_4 alkoxy, C_2-C_4 alkenyloxy, phenoxy, benzyloxy, and amino, wherein the individual ring size is 5-6 members, and wherein the heterocyclic ring contains 1-6 heteroatom(s) independently selected from the group consisting of O, N, and S.

23. The method of claim 1, wherein the mammal is human.

24. The method of claim 1, wherein the nerve-related vision disorder is retinal ischemia.

25. The method of claim 24, wherein the retinal ischemia is selected from the group consisting of degeneration of retinal ganglion cells, degeneration of optic nerve axons, degeneration of myelin sheaths, ischemic optic neuropathy, and retinal vascular blockage.

26. The method of claim 1, wherein the nerve-related vision disorder is optic nerve transection.

27. The method of claim 26, wherein the optic nerve transection is selected from the group consisting of ganglion cell death after optic nerve transection and myelin degeneration after optic nerve transection.

28. The method of claim 1, wherein the nerve-related vision disorder is diabetes.

29. The method of claim 28, wherein the diabetes is selected from the group consisting of diabetes from degeneration and diabetic retinopathy.

30. The method of claim 1, wherein the nerve-related vision disorder is macular degeneration.

31. The method of claim 1, wherein the nerve-related vision disorder is glaucoma related degeneration.

32. The method of claim 1, wherein the nerve-related vision disorder is cataract related degeneration.

33. The method of claim 1, wherein the nerve-related vision disorder is a detached retina.

34. The method of claim 1, wherein the nerve-related vision disorder is inflammation related degeneration.

35. The method of claim 1, wherein the nerve-related vision disorder is photoreceptor degeneration.

36. The method of claim 1, wherein the nerve-related vision disorder is optic neuritis.

37. The method of claim 1, wherein the nerve-related vision disorder is dry eye degeneration.

Addendum A

The Journals of GERONTOLOGY

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Volume 46, Number 6

CONTENTS

November 1991

(continued from outside back cover)

Journal of Gerontology: PSYCHOLOGICAL SCIENCES

Journal of Gerontology: SOCIAL SCIENCES

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(Required by 39 U.S.C. 3685)

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Journal of Gerontology: PSYCHOLOGICAL SCIENCES
1991, Vol. 46, No. 6, P372-377

Imipramine in the Treatment of Depressed Alzheimer's Patients: Impact on Cognition

Linda Teri,[1] Burton V. Reifler,[1] Richard C. Veith,[1,3] Robert Barnes,[1,3] Emily White,[2] Pamela McLean,[1] and Murray Raskind[1]

Departments of [1]Psychiatry and Behavioral Sciences, and [2]Epidemiology, University of Washington.
[3]Geriatric Research, Education and Clinical Center, Seattle Veterans Administration Medical Center.

A double-blind study evaluated the impact of imipramine on cognitive function in 61 patients with Alzheimer's disease. Twenty-eight patients had coexistent depression and dementia; 33 had dementia only. All were randomly assigned to an 8-week trial of imipramine or placebo. For both depressed and nondepressed subjects, the effect of imipramine on cognition was minimal. A subtle decrement in general cognitive function was evident in those treated with imipramine, as compared with those treated with placebo. No effects were observed on memory. Clinicians are advised that very low doses of imipramine (25 mg/daily) may be tolerated in depressed Alzheimer patients, but that cognitive changes do occur in some patients and should be carefully monitored.

DEMENTIA of the Alzheimer's type (DAT) is the most prevalent form of dementia, affecting almost two million people in the United States (Katzman et al., 1983). Approximately 30% of these patients are also likely to suffer from depressive symptoms, adding problems such as dysphoric mood, sleep and appetite disturbances, decreased interest and energy, and suicidal thoughts and feelings of worthlessness to their cognitive and functional impairment (cf. Reifler, Larson, & Teri, 1987). Although these figures suggest that approximately 700,000 older adults are thus affected, surprisingly little is known about ways to help these patients.

Depression may well be a treatable component of DAT. Depression in nondemented older adults has been shown to respond well to both pharmacological (Branconnier et al., 1983; Grauer & Kral, 1960; Veith et al., 1982) and nonpharmacological (Gallagher & Thompson, 1983) interventions. However, use of the former is not without risk. It has been well documented in the literature that older adults metabolize pharmacological agents more slowly than do younger adults, are at greater risk for developing adverse side effects or acute toxic reactions, and are more likely to have multiple medical diseases and medications that can complicate antidepressant medication treatment (cf. Salzman & Shader, 1979). In patients with DAT, medication effects are particularly worrisome. The anticholinergic effects of common antidepressants [such as the tricyclic antidepressants (TCAs)] may serve to exacerbate cognitive deficits in nondemented adults (cf. Chesrow et al., 1964; Davies, Tucker, Harrow, & Detre, 1971; DiMascio, Heninger, & Klerman, 1964), and patients with DAT already demonstrate loss of cholinergic neuronal function (Bartus, Dean, Beer, & Lippa, 1982; Davies & Maloney, 1976; Sunderland et al., 1987; Whitehouse, Price, Struble, Clark & Gyle, 1982). TCAs may, therefore, add to DAT patients' cognitive impairment. Exacerbation of cognitive deficits because of TCAs, however, is by no means certain. In nondemented, younger depressives, TCAs have been found to yield improved cognitive functioning, thought to be explained by the improvement in depression (Glass, Uhlenhuth, Hartel, Matuzas, & Fischman, 1981). However, the nature of cognitive impairment in depression is most likely different from that found in DAT (LaRue, D'Elia, Clark, Spar, & Jarvik, 1986), and not all types of memory impairment are affected by therapeutic success (Legg & Stiff, 1976; Sternberg & Jarvik, 1976). Further, current controversy exists regarding the prevalence of patients likely to be affected by anticholinergic effects and the dose at which such effects are seen (cf. Goldstein, Birnbom, & Laliberte, 1982; Schulterbrandt, Raskin, & Reatig, 1974). A recent review of the use of TCAs in cognitively impaired elderly subjects concluded that, although "cognitive dysfunction is often observed in elderly depressed patients" and although "TCAs can cause measurable deficits" in cognition, TCAs "tend to produce clinical improvement" and are, therefore, to be strongly considered in the treatment of depression in demented adults (Cole, Branconnier, Salomon, and Dessain, 1983, pp. 14 and 19). One additional study not included in that review also supports that position. In a retrospective chart review of antidepressant medication use with 20 elderly dementia patients, Reifler, Larson, Teri, and Poulsen (1986) reported that 17 patients (85%) had reported an improvement in mood, vegetative symptoms, and activities in daily living.

The present study is part of a larger investigation (Reifler et al., 1989) designed to evaluate the effectiveness of imipramine in the treatment of depression in patients with DAT. DAT patients with and without depression participated in a double-blind, placebo-controlled trial of the TCA, imipramine. Results indicated that patients with depression and DAT improved significantly over time on pre- to posttesting on the Hamilton Depression Scale scores. However, patients treated with imipramine did not do significantly better than those treated with placebo. These results, coupled with the knowledge that imipramine is known to block central cholinergic receptors and therefore may exacerbate the cholinergic deficiency of DAT (Snyder & Kamamura, 1977), under-

score the importance of evaluating whether imipramine adversely affects cognition in DAT patients.

METHOD

Subjects. — The subjects were selected from two University of Washington outpatient clinics: the Geriatric and Family Services at the University Hospital (Reifler, Larson, & Teri, 1987) and the Geriatric Research, Education, and Clinical Center Clinic at the Seattle Veterans Administration Medical Center.

All subjects sought or were referred for evaluation and treatment of their cognitive and effective difficulties, and met the following criteria:

1. Agreement by two examiners, blind to each other's assessment, that
   a. the subject met DSM-III (American Psychiatric Association, 1980) criteria for Primary Degenerative Dementia (PDD), and
   b. The subject did (or did not) meet DSM-III criteria for Major Depressive Disorder (MDD). Agreement between raters, calculated as the number of agreements divided by the number of evaluations, yielded an agreement level of 84%.
2. Mini-Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975) score of 25 or less for all subjects.
3. Hamilton Depression Scale Score (Hamilton, 1967) of 15 or above for those subjects diagnosed as depressed.
4. Availability of a family member to serve as a coparticipant, and informed consent needed from both subject and coparticipant.

Of 144 subjects who met the above criteria, 75 were excluded because of one or more of the following:

1. Depression was judged to be too severe to permit outpatient treatment ($n = 2$).
2. Unwillingness or inability to discontinue any other psychotropic or cognitive-enhancing medications ($n = 22$).
3. Medical or medication contraindications to the use of imipramine, such as the presence of conduction defects on EKG ($n = 35$).
4. Presence of any diagnosis in addition to PDD and/or MDD that could influence (or cause) the subject's cognitive or affective distress (such as hypothyroidism and delirium) ($n = 16$).

A total of 69 subjects were enrolled in the study. Of these, eight terminated prior to week 6 of the treatment phase and were therefore excluded from analyses. A total of 61 subjects completed this study.

Procedure. — Subjects in each diagnostic group (PDD with Depression, PDD without Depression) were randomly assigned to one of two 8-week-long treatment conditions: imipramine or placebo. Both imipramine and placebo were provided courtesy of Ciba-Geigy in identical-appearing tablets containing 25 mg of imipramine HCl or placebo. Initial dose was 25 mg daily, with dosage increased weekly in 25 mg increments until there was evidence of a therapeutic response or until side effects prevented further increases. Mean daily dosage at completion of treatment was 83 mg for depressed patients and 82 mg for nondepressed patients. The depressed group had a total plasma level at completion of the study of 119 ng/ml (72 ng/ml imipramine plus 47 ng/ml desipramine), while the nondepressed group had a total of 132 ng/ml (86 ng/ml imipramine plus 48 ng/ml desipramine). These levels were within generally accepted therapeutic ranges (Hollister, 1978).

Assessments were conducted pre- and posttreatment. Thus, the study is a 2 × 2 × 2 repeated measures design: diagnosis (PDD with Depression, PDD without Depression) by treatment condition (imipramine, placebo) over time (pre, post).

Table 1 summarizes the demographic characteristics of subjects in each condition. No significant differences were obtained between treatment conditions for either diagnostic group on any of the demographic variables [*DAT and Depression:* age ($F(1,26) = 2.89$, NS); gender (χ^2 ($n = 28$) = .30, NS); marital status (χ^2 ($n = 28$) = .67, NS); *DAT only:* age ($F(1,31) = .86$, NS); gender (χ^2 ($n = 33$) = .0, NS); marital status (χ^2 ($n = 33$) = .54, NS)].

Measures. — This study focused on the measures of cognitive status obtained as part of the larger treatment outcome study. The MMSE (Folstein et al., 1975), already discussed as a screening measure for inclusion into this study, was administered to each patient. Originally, the Wechsler Adult Intelligence Scale–Revised (WAIS-R) was to be administered to all patients; however, after eight subjects, we switched to the Dementia Rating Scale (Coblentz et al., 1973), a more detailed measure of cognitive status to reduce the time requirements and possibility of subject fatigue. In addition, the Fuld Object Memory Evaluation (FOME) (Fuld, 1982) and portions of the Wechsler Memory Scale (Wechsler, 1945) were administered to a subset of patients ($n = 54$) who were significantly less cognitively impaired (MMSE: $F(1,59) = 22,31$, $p < .001$), thereby able to complete additional testing. Patients who received these additional measures did not differ significantly from the seven other patients on age ($F(1,59) = 3.78$,

Table 1. Demographic Characteristics of Alzheimer's Patients

	DAT and Depression		DAT Only	
	Imipramine	Placebo	Imipramine	Placebo
n	13	15	14	19
Age × (*SD*)	76 (7)	71 (9)	68 (7)	71 (8)
Gender				
Female	10	9	7	10
Male	3	6	7	9
Informant				
Spouse	4	7	10	13
Child	8	6	1	4
Other	1	2	3	2
Marital status				
Married	4	8	12	13
Widowed	9	7	2	6
Education level				
Some high school	4	2	2	1
High school graduate	4	4	1	1
Some college	4	6	7	15
Graduated college	1	3	4	2

NS) or on level of depression [Hamilton Depression Rating Scale (HDRS): $F(1,59) = .07$, NS]. The limited number of subjects who did not complete these measures precluded additional analyses of other demographic or diagnostic data.

The Mini-Mental State Exam. — The MMSE (Folstein et al., 1975) is a measure of cognitive status evaluating orientation, attention, immediate memory, language, and praxis. It yields a total score (0–30), with scores below 24 considered indicative of cognitive dysfunction (Anthony, LeResche, Niaz, VonKorff, & Folstein, 1982).

The Dementia Rating Scale (cDRS). — The cDRS (Coblentz et al., 1973) evaluates many of the cognitive domains identified as critical to accurate classification of DAT by the recent NINCDS-ADRDA Work Group (McKhann et al., 1984). In Albert's (1982) review of geriatric neuropsychology, the cDRS is cited as an excellent tool for evaluating a wide variety of cognitive functions in DAT patients. It yields a total score (0–144) and five subscale scores [attention (0–37), initiation and perseveration (0–37), construction (0–6), conceptualization (0–39), and memory (0–25)]. The cDRS provides good discriminate validity between normal and cognitively impaired groups, good overall reliability, and a strong correlation with overall patient functioning (Mattis, 1976; Prinz et al., 1983; Vitaliano el al., 1984).

The Wechsler Memory Scale (WMS). — Two subtests of the WMS (Wechsler, 1945, 1981), Logical Memory (LM) and Associate Learning (AL), were administered to evaluate the degree to which immediate memory and new learning may be affected by imipramine. Scores were calculated according to the *WMS Standardization Manual* (Wechsler, 1981): LM = the number of phrases recalled in two 23-item paragraphs/2; AL = the number of 6 easy word pairs learned/2 + the number of 4 hard word pairs learned. Scores for LM range from 0 to 23, and scores for AL range from 0 to 7.

The Fuld Object Memory Evaluation. — The FOME (Fuld, 1981) was specifically developed to assess memory in older adults. It was administered and scored according to instructions provided by Fuld (1981) with recall trials of 10 common objects alternated with a selective reminding procedure and 60 seconds of category naming. The overall score, a "retention estimate," is calculated by summing the total number of objects recalled with the total number of items recognized. Scores range from 0 to 10.

RESULTS

A potential confound in this study is that the effect of imipramine on cognition may be obscured by its impact on depression. That is, patients may improve on cognitive tests because of their improvement in depression, not because of imipramine itself. As stated previously, this is not an issue here because although all patients improved pre to post, patients treated with imipramine did not improve significantly more than those treated with placebo. Thus, "treatment improvement" was essentially controlled. For a complete discussion of the depression-related treatment findings, refer to the data by Reifler et al., (1989). Summary HDRS scores and statistical results are presented here for information only (see Table 2).

Table 3 summarizes the pre, post, and change scores on the cognitive measures for all subjects. For all measures, lower scores represent more impaired cognitive function; lower change scores represent less improvement pre- to postassessment.

Patients with DAT only scored lower on all pretest measures than did patients with DAT and depression (MMSE: $F(1,59) = 5.31$, $p < .05$; HDRS: $F(1,59) = 220.38$, $p < .001$; cDRS total: $F(1,51) = 7.37$, $p < .01$). This was expected, given earlier findings that depression in DAT is associated with milder levels of cognitive impairment. Because of this, and because the two diagnostic groups were inherently different (by virtue of their diagnosis), data for these groups were analyzed separately.

A univariate, as opposed to multivariate, approach was conducted consistent with the recommendations of Vitaliano (1982) and because our a priori goal was to examine the impact of imipramine on specific types of cognitive function. Pretest scores were first analyzed to determine if randomization across treatment groups was successful. Analysis of variance (ANOVA) for pretest scores (conducted independently across the two diagnostic groups) indicated randomization was successful. No significant differences between treatment conditions on any dependent measures were obtained [*DAT and Depression* — MMSE: $F(1,26) = .30$, NS; cDRS total: $F(1,18) = .54$, NS; WMS-AL: $F(1,22) = .01$, NS; WMS-LM: $F(1,22) = .26$, NS; FOME: $F(1,22) = .06$, NS; *DAT Only* — MMSE: $F(1,31) = .42$, NS; cDRS total: $F(1,31) = 2.24$, NS; WMS-AL: $F(1,23) = 1.44$, NS; WMS-LM: $F(1,29) = 1.96$, NS; FOME: $F(1,26) = .48$, NS].

ANOVA was therefore conducted for each dependent measure of cognitive function with time and treatment condition, the independent variables.

DAT and depression. — MMSE scores yielded a significant main effect for time ($F(1,26) = 6.59$, $p < .01$), but not for treatment condition ($F(1,26) = .15$, NS) nor for the

Table 2. Means and Standard Deviations of Hamilton Depression Scale on Patients Pre- and Postintervention

	Pre	Post
DAT and depression		
Imipramine	19.3 (3.5)	11.5 (3.7)
Placebo	18.6 (4.0)	10.8 (3.5)
DAT only		
Imipramine	6.9 (2.9)	7.9 (3.1)
Placebo	6.8 (2.4)	6.5 (1.8)
Time:	$F(1,57) = 61.16$	
Treatment × Time:	$F(1,57) = .81$	
Diagnosis × Time:	$F(1,57) = 84.36$*	
Treatment × Diagnosis × Time:	$F(1,57) = .54$	

*$p < .001$.

Table 3. Means and Standard Deviations of Cognitive Measures on Patients' Pre, Post, and Change Scores

		Pre	Post	Change
DAT and DEPRESSION				
Mini-Mental Status Exam				
Imipramine	(n = 13)	16.9 (4.6)	18.7 (5.4)	1.9
Placebo	(n = 15)	18.0 (5.5)	19.3 (6.5)	1.3
Dementia Rating Scale				
Total				
Imipramine	(n = 12)	111.2 (14.3)	104.3 (20.9)	−6.9
Placebo	(n = 9)	115.9 (14.3)	117.4 (13.7)	1.5
Attention				
Imipramine		35.4 (1.6)	35.5 (1.7)	.1
Placebo		35.7 (.9)	35.7 (1.0)	0
Initiation and perseveration				
Imipramine		25.7 (7.2)	23.7 (7.9)	−2.0
Placebo		27.0 (4.9)	26.8 (8.1)	−.2
Construction				
Imipramine		4.9 (2.4)	4.5 (2.5)	−.4
Placebo		6.9 (1.9)	6.9 (1.8)	0
Conceptualization				
Imipramine		32.2 (5.8)	26.7 (8.6)	−5.6
Placebo		33.1 (7.0)	33.0 (10.1)	−.1
Memory				
Imipramine		13.5 (3.9)	13.5 (4.3)	0
Placebo		15.7 (4.6)	16.4 (4.3)	.7
Weschsler Memory Scale				
Associate learning				
Imipramine	(n = 10)	7.8 (2.9)	7.6 (2.3)	−.2
Placebo	(n = 12)	7.9 (1.5)	8.0 (2.7)	.2
Logical memory				
Imipramine		2.9 (2.3)	3.7 (1.6)	.8
Placebo		3.3 (2.4)	3.1 (2.3)	−.3
Fuld Object Memory Evaluation				
Imipramine	(n = 12)	7.8 (2.5)	7.7 (2.9)	−.1
Placebo	(n = 12)	8.1 (2.6)	8.7 (2.5)	.7
DAT only				
Mini-Mental Status Exam				
Imipramine	(n = 14)	13.4 (6.9)	13.1 (7.7)	−.3
Placebo	(n = 19)	14.8 (5.1)	15.1 (6.2)	.3
Dementia Rating Scale				
Total				
Imipramine	(n = 14)	80.4 (44.6)	72.7 (43.8)	−7.6
Placebo	(n = 19)	98.6 (24.8)	98.1 (26.4)	−.5
Attention				
Imipramine		27.7 (11.9)	25.2 (12.9)	−2.5
Placebo		33.4 (5.1)	33.9 (4.2)	.5
Initiation and Perseveration				
Imipramine		16.9 (10.8)	13.9 (10.4)	−3.0
Placebo		22.0 (8.1)	20.2 (7.9)	−1.8
Construction				
Imipramine		3.7 (2.8)	3.5 (2.8)	−.2
Placebo		4.9 (1.8)	4.7 (2.0)	−.2
Conceptualization				
Imipramine		23.6 (15.6)	22.1 (15.0)	−1.5
Placebo		27.6 (10.1)	28.7 (11.4)	1.1
Memory				
Imipramine		8.5 (5.3)	8.1 (5.2)	−.4
Placebo		10.6 (4.3)	10.4 (6.0)	−.2
Wechsler Memory Scale				
Associate learning				
Imipramine	(n = 11)	4.8 (3.8)	6.3 (3.6)	1.5
Placebo	(n = 16)	6.3 (2.0)	6.2 (1.6)	−.1
Logical memory				
Imipramine		1.3 (1.5)	1.5 (1.6)	.2
Placebo		2.2 (2.1)	2.3 (2.2)	.2
Fuld Object Memory Evaluation				
Imipramine	(n = 10)	7.4 (3.1)	7.2 (2.5)	−.2
Placebo	(n = 18)	6.7 (2.4)	6.5 (2.4)	−.2

interaction of treatment condition by time ($F(1,26) = .23$, NS). Thus, although patients in both treatment conditions improved from pre- to posttest, these gains were not significantly different across conditions. Improvement in MMSE scores for both conditions averaged between one and two points (see Table 3).

On the cDRS, no significant main effects were obtained for time ($F(1,18) = 1.42$, NS), treatment condition ($F(1,18) = 1.74$, NS), nor time by treatment condition interaction ($F(1,18) = 2.62$, $p < .15$). Examination of mean scores indicated that there was a consistent pattern for patients in the imipramine condition to decline more in total cDRS score than patients in the placebo condition. ANOVA of subscale change scores (calculated as post- minus pretest scores) indicated that no one subscale accounted for this trend (overall Hotellings $F(5,14) = .45$, NS), although examination of mean score on each subscale indicated that patients in the imipramine condition performed worse over time than patients in the placebo condition. This was particularly striking on the subscale, conceptualization, where the mean change for imipramine was −5.6 as compared with −.1 for placebo. However, this difference did not attain statistical significance ($F(1,18) = 2.48$, $p < .15$).

On both subscales of the WMS, no significant main or interaction effects were found [*WMS-AL* — Time: $F(1,20) = .10$, NS; Treatment: $F(1,20) = .07$, NS; Time × Treatment: $F(1,20) = .29$, NS; *WMS-LM* — Time: $F(1,21) = .37$, NS; Treatment: $F(1,21) = .01$, NS; Time × Treatment: $F(1,21) = 2.72$, NS]. As can be seen from Table 3, mean change scores were quite small and did not indicate any pattern of change.

On the FOME, no significant main or interaction effects were found (Time: $F(1,22) = 1.04$, NS; Treatment: $F(1,22) = .31$, NS; Time × Treatment: $F(1,22) = 1.84$, NS). Similar to the WMS, mean change scores were quite small and did not indicate any pattern of change.

DAT only. — On the MMSE, no significant main effects for time ($F(1,31) = .02$, NS), treatment condition ($F(1,31) = .55$, NS), or time by treatment interaction were obtained ($F(1,31) = .48$, NS).

On the cDRS total score, a significant main effect for time ($F(1,31) = 7.27$, $p < .01$) was obtained, as well as for time by treatment condition ($F(1,31) = 7.16$, $p < .01$); no significant main effect was obtained for treatment condition, although a trend was obtained ($F(1,31) = 3.22$, $p < .10$). From pre- to postassessment, an average decline of 8 points was obtained for patients in the imipramine condition as compared with an average decline of one-half point for patients in the placebo condition. Examination of the subscale scores revealed a consistent pattern for mean scores on each subscale to be lower in the imipramine condition than in the placebo condition (see Table 3). Multivariate analysis of variance (MANOVA) of these subscale scores indicated a significant overall effect (Hotellings $F(5,27) = 3.69$, $p < .01$) consistent with the earlier ANOVA as expected and explained by significant effects for two subscales: attention ($F(1,31) = 11.15$, $p < .01$) and conceptualization ($F(1,31) = 5.00$, $p < .04$). This pattern of results is consistent with

that obtained on the cDRS in the Depressed DAT group, although those results did not attain statistical significance.

Also consistent with the results in the Depressed DAT group, no significant main effects or interaction effects were obtained on the WMS subscales or the FOME. [*WMS-AL* — Time: $F(1,22) = 1.84$, NS; Treatment: $F(1,22) = .16$, NS; Time × Treatment: $F(1,22) = 3.56$, $p < .10$; *WMS-LM* — Time: $F(1,28) = .51$, NS; Treatment: $F(1,28) = 1.47$, NS; Time × Treatment: $F(1,28) = .02$, NS; *FOME* — Time: $F(1,26) = .58$, NS; Treatment: $F(1,26) = .31$, NS; Time × Treatment: $F(1,26) = 0$, NS]. This was also consistent with results on the MMSE.

Discussion

The goal of this study was to investigate the impact of the antidepressant medication, imipramine, on cognition in Alzheimer's patients. Patients (with and without depression) were treated with imipramine and compared with those treated with placebo over an 8-week period. Results indicate a complex pattern. On the MMSE, a measure of global cognitive function (a statistically significant improvement in cognition) was obtained for depressed DAT patients on imipramine and placebo, but the amount of change was minimal; no statistically significant change (on the MMSE) was obtained for nondepressed patients on imipramine or placebo. On the cDRS, a more sensitive measure of cognitive function (a statistically significant decline in cognition) was obtained for nondepressed DAT patients on imipramine. Depressed DAT patients did not demonstrate significant decline (on the cDRS), although mean scores followed the same pattern. In both groups, however, the range of choice was small and of questionable clinical significance. No significant difference on cDRS was obtained for depressed and nondepressed DAT patients on placebo. On the two tests of memory, the FOME and WMS, no significant differences were obtained nor were any patterns of decline or improvement suggested.

In summary, the effect of imipramine on cognition in DAT patients seems minimal. The patient group most likely to suffer adverse effects were those least likely to receive treatment (nondepressed patients). Indeed, the term adverse effects for the findings obtained here is misleading, as the effects were often mild and of questionable clinical importance.

There are a number of questions that must be answered before these findings can be interpreted. First, are there any methodological biases that may explain these findings? Second, are there any substantive clinical or conceptual explanations for them? Regarding potential methodological biases, this population of Alzheimer's patients was selected from an outpatient geriatric clinic and, consequently, may not be representative of the larger Alzheimer's population. It is likely that these patients and caregivers were more troubled since they were seeking help. However, it is unlikely that this created a significant bias in this study because, within this sample, patients were randomly assigned to treatment conditions, and analyses of pretest scores indicated that treatment groups were not dissimilar at the start of treatment.

The changes obtained on cognitive function were clinically quite subtle, representing mild changes, and are likely to be of minimal clinical significance. However, in this study, the initial imipramine dose was very low (25 mg/daily) and increased slowly, with the average dose for our sample being 82 mg/daily. Our findings may have been more dramatic at higher doses because higher doses may have more anticholingeric effects and therefore more adversely affect cognition. Thus, the safest clinical course when prescribing these drugs to older adults is one of caution (as has been advocated by others, e.g., Salzman, 1985) but not avoidance. Clinicians should consider both pharmacological and nonpharmacological intervention for depression in Alzheimer's patients.

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